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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/696,909
Filing Date: October 29, 2003
Appellant(s): LORENS ET AL.

Susan W. Graf
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 3, 2011 appealing from the Office action mailed November 5, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal No. 2009-011194, decided by the Board of Patent Appeals and Interferences (BPAI) on March 16, 2010.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1, 14-18, 27, 41-44, 54, and 55.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

1. Frater-Schroder et al., Proc. Natl. Acad. Sci. USA 84:5277-5261, 1987.

2. Healy et al., Am. J. Physiol. Lung Cell Metabol. 280:L1273-L1281, 2001.

3. Klinghoffer et al., U.S. Pat. App. Publ. No. 2004/0077574, May 23, 2002.

4. Mor, U.S. Pat. App. Publ. No. 2003/0157573, Feb. 12, 2002.

5. O'Donnell et al., Am. J. Pathol. 154:1171-1180, 1999.

6. Varner and Cheresh, Curr. Opin. Cell Biol. 8:724-730. 1996.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The rejection of claims 1, 14-18, 27, 41-44, 54, and 55 under 35 U.S.C. 103(a) as being unpatentable over Mor, O. (US Pat. App. Pub. 2003/0157573 A1 Feb. 12, 2002) further in view of Klinghoffer et al. (United States Patent Application Publication No.: 2004/0077574, May 23, 2002, previously cited), further in view of O'Donnell et al. (Am. J. Path. 1999, 154: 1171-1180, IDS item), and, further in view of Varner and Cheresh (Current Opinion in Cell Biology, October 1996, 8:724-730, previously cited) is maintained for the reasons of record.

Mor teaches identifying an inhibitor of Axl by determining the ability of compounds such as antibodies, antisense molecules, and small organic molecules to inhibit the Axl kinase activity in cells, like endothelial cells, expressing endogenous or human Axl, which comprises SEQ ID NO: 4, determining the inhibition of Axl kinase activity in vitro, and by determining cell

survival, cell differentiation, or cell proliferation response to the compound. See claims 1-19, 21-23, and 35, Abstract, ¶ 0020, 0022, 0033-0036, 0045, 0046, 0049-0064, 0108, 0249, 0255, and Appendix 1 and 2. Mor teaches determining decreases in expression of the Axl polypeptide in response to the compounds. See ¶ 0065. Mor teaches that the identified drugs may be used as anti-angiogenic drugs for the treatment of cancer by preventing or reducing the proliferation of endothelial cells. See ¶ 0090.

Mor teaches as set forth above, and teaches that activation of Axl increases the survival of endothelial cells and induces migration of vascular muscle cells, but does not specifically teach using RNAi as a compound or assaying $\alpha V\beta 3$ expression, tube formation, or haptotaxis.

Klinghoffer et al. teach that siRNA/RNAi polynucleotides offer advantages over other types of polynucleotides for sequence specific alteration of gene expression including lower effective siRNA/RNAi polynucleotide concentration, enhance stability, shorter lengths, they are readily taken up by intact cells, and are effective at concentration that are several orders of magnitude lower than those required for either antisense or ribozyme polynucleotides, see paragraph 0022 and 0025.

O'Donnell et al. teach that Axl exhibits homophilic binding via its extracellular domain, which could be relevant to tube formation in angiogenesis. See p. 1176-2nd col. O'Donnell et al. teach that the ligand of Axl, Gas6, has multiple properties relevant to vascular biology including promoting adhesion of Axl expressing cells and stimulation of chemotaxis of vascular smooth muscle cells. See p. 1177-2nd col.

Varner and Cheresh teach that integrin $\alpha V\beta 3$ is significantly upregulated on vascular cells within human tumors and in response to growth factors and plays a biological role in a

critical event of blood vessel formation during tumor angiogenesis by promoting vascular cell survival and that inhibition of αVβ3 inhibits angiogenesis, see section on Role of Integrins in Tumor Angiogenesis, p. 726- 727.

It would have been prima facie obvious at the time the invention was made to combine teachings of Mor and Klinghoffer et al. and use RNAi molecules in the screening methods of Mor because Klinghoffer et al. teach the advantages of siRNA as inhibitory molecules and one would have been motivated to identify the most effective inhibitory molecule in the screens of Mor to identify the most effective anti-angiogenic drug. Given that screening assays are routinely performed in the art, one of skill in the art would have a reasonable expectation of success of making and using the claimed assay.

Additionally, it would have been prima facie obvious at the time the invention was made to combine teachings of Mor, O'Donnell et al., and Varner and Cheresh and measure αVβ3 expression or tube formation in endothelial cells in response to the test compounds because Mor teaches assaying cellular differentiation in the screening assays for identifying angiogenesis inhibitors, O'Donnell et al. teaches that Axl may be involved in tube formation during and angiogenesis, and Varner and Cheresh teach that αVβ3 expression plays is critical event of blood vessel formation during tumor angiogenesis, αVβ3 is important endothelial cell survival (like Axl), and inhibition of αVβ3 inhibits angiogenesis.

(10) Response to Argument

Appellants argue that the analysis for determining obviousness under 35 U.S.C. § 103(a), as articulated in Graham v. John Deere Co. 383 U.S. 1 (1966), requires 1) determining the scope and content of the prior art; 2) ascertaining the differences between the prior art and the claims at

issue; and 3) resolving the level of ordinary skill in the pertinent art. Graham, 383 U.S. at 7. In particular, ascertaining the differences between the prior art and the claims requires that both the claims and the prior art be read as a whole (M.P.E.P. § 2141.02; In re Langer, 465 F.2d 896, 899, 175 USPQ 169, 171 (CCPA 1972); W.L. Gore & Associates v. Garlock, Inc., 721 F.2d 1540, 1551, 220 USPQ 303,311 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)). "All of the disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art... [W]hen 'all of the disclosures in a reference' are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference." In re Langer, 465 F. 2d at 899, 175 USPQ at 171.

Appellants argue that to establish a prima facie case of obviousness, the Office must establish that (1) there is some suggestion or motivation to combine the references, either in the references or in common general knowledge of one of skill in the art (MPEP § 2143.01); and (2) there is a reasonable expectation of success (MPEP § 2143.02). In addition, the Office must show that the references teach or suggest all claim limitations. "When determining whether a claim is obvious, an Examiner must make 'a searching comparison of the claimed invention - including all its limitations - with the teaching of the prior art.' Thus, 'obviousness requires a suggestion of all limitations in a claim.'" Ex parte Mumper BPAI, Appeal No. 2008-2332, June 27, 2008.

Appellants argue that the Office asserts that Mor specifically teaches that compounds identified in the assays disclosed in that reference could be used as anti-angiogenic drugs, that O'Donnell et al. show that Axl is expressed in endothelial cells and is involved in their viability and survival, and that Varner and Cheresh teach that $\alpha V\beta 3$ is important in endothelial cell

survival (Office action of November 5, 2010, page 6, second full paragraph). The Office asserts that, "given the art teaches that these are important aspects of angiogenesis by endothelial cells, it would have been obvious to one of skill in the art to assay these function in an effort to identify an angiogenesis inhibitor in addition to assaying a test compound's effect on Axl activity, given that they both have a role in endothelial cell function and angiogenesis" (Office action of November 5, 2010, page 6, second full paragraph).

Appellants argue that the Office also states that Klinghoffer et al. disclose that siRNA is an advantageous inhibitory molecule. The Office asserts that it would have been obvious to one of skill in the art to "combine the teachings of Mor and Klinghoffer et al. and use RNAi molecules in the screening methods of Mor...to identify the most effective inhibitory molecule..." (Office action of November 5, 2010, page 4, first full paragraph).

Appellants argue that, when read as a whole, neither Mor nor O'Donnell et al. (nor any of the references used to support this rejection) teach or suggest that Axl plays a role in angiogenesis, and therefore one of skill in the art would not be motivated to utilize the method of Mor to identify a compound that inhibits angiogenesis (for example by assaying tube formation, haptotaxis, or $\alpha V\beta 3$ expression). Furthermore, one of skill in the art would not have had a reasonable expectation of success in combining these references to arrive at Applicants' claimed method. Thus, the Office has not met the burden needed to support a prima facie case of obviousness for claims 1, 14-18, 27, 41-44, 54, and 55 on the basis of the cited references.

A. No Motivation to Combine the References

Appellants argue that "Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so." M.P.E.P. § 2143.01. As discussed above, the Office asserts that one of skill in the art would be motivated to combine the cited references to identify a compound that inhibits angiogenesis.

Appellants argue that the rationale to combine the prior art "may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law." M.P.E.P. § 2144. In this case, there is no rationale to combine the references, particularly when the references are read as a whole, as required by case law and the M.P.E.P (discussed above).

Appellants argue that the focus of Mor is on identification of genes which have changes in expression in renal pathologies, and use of these sequences for screening for treatment modalities for fibrosis in general, and specifically renal fibrosis and glomerulosclerosis (paragraph [0002], Field of the Invention). Mor discloses a method for identifying compounds for treating renal disease (specifically diabetic nephropathy), fibrosis (particularly renal fibrosis) and glomerulosclerosis (see, e.g., paragraphs [0002], [0032-0033], [0036], [0041], and [0096]). Mor discloses that Axl expression is increased in fibrotic kidney in humans and in animal models of renal fibrosis (e.g., paragraphs [0240] and [0249-0250]), and suggests that therapeutic approaches aimed at Axl would be beneficial for both chronic and acute renal failure (paragraph [0251]). Thus, taken as a whole, Mor is directed to the role of Axl in renal pathology, and more specifically, renal fibrosis.

Appellants argue that in addition, the assays disclosed in Mor that measure the effect of a test compound on a cellular phenotype assess cell survival, cellular differentiation, or cell

proliferation (paragraph [0059]). Specific assays include proliferation of mesangial cells, renal fibroblasts, or renal tubular cells, collagen deposition in the extracellular matrix of renal fibroblasts, and transdifferentiation of renal tubular cells to myofibroblasts (paragraph [0069]). Thus the focus of Mor is also on the possible role of Axl in cell proliferation or survival.

Appellants argue that the Office points to paragraph [0090] of Mor as teaching that compounds identified in the disclosed assays for inhibition of Axl may be used as anti-angiogenic drugs. Mor specifically states that the identified compounds "may also be used as anti-angiogenic drugs for the treatment of cancer and other conditions where preventing or reducing proliferation of endothelial cells is desired" (paragraph [0090], emphasis added). Appellants argue and emphasize that this single sentence is the only mention of angiogenesis in the entirety of the Mor reference (the specification is 20 pages long). Furthermore, Mor states that a compound that inhibits Axl may prevent or reduce proliferation of endothelial cells. One of skill in the art would recognize that a compound may reduce proliferation of endothelial cells without being anti-angiogenic (see, e.g., Frater-Schroder et al., Proc. Natl. Acad. Sci. USA 84:5277-5281; page 5277, col. 2, first paragraph; discussed in detail in Section B, below). In addition, Mor analyzed the expression of Axl in the rat and found that Axl is widely expressed in many tissues and cell types, including intestinal tract, skin, salivary gland, heart, prostate, liver portal tract (fibroblasts and histiocytes/macrophages), spleen, lymph node, thymus, lung (macrophages and/or lymphocytes), liver sinusoidal cells (endothelial, stellate, and Kuppfer cells), testis (Sertoli cells and germ cells), and brain (glial cells) (paragraphs [0252-0257]). This pattern of expression in a wide variety of tissues and cell types would not suggest to one of skill in the art that Axl is involved in angiogenesis. Given the overall teaching of Mor that Axl is

involved in renal pathology (particularly fibrosis) and is widely expressed, one of skill in the art would not consider that Mor suggests that Axl is involved in angiogenesis. At most, one of skill in the art would be led to conclude that Axl may be involved in cell proliferation and that the assays described in Mor may be used to identify inhibitors of cell proliferation.

Appellants argue that the Office relies on O'Donnell et al. to provide motivation to measure tube formation in the assay of Mor (Office action of November 5, 2010, page 4, second full paragraph) and motivation to identify anti-angiogenic compounds because Axl is expressed in endothelial cells and is involved in their viability and survival (Office action of November 5, 2010, page 6, second full paragraph).

Appellants argue that O'Donnell et al. disclose that Axl is expressed in synovial tissue from patients with rheumatoid arthritis, particularly in endothelial cells in subsynovial capillaries, smooth muscle cells in arterioles and veins, and synovial lining cells (e.g., page 1173, col. 2 to page 1174, col. 1). O'Donnell et al. also disclose that the Axl ligand Gas6 increases endothelial cell survival and/or reduces endothelial cell apoptosis in response to growth factor depletion or treatment with tumor necrosis factor α (abstract; page 1174, col. 2 to page 1176, col. 1). O'Donnell et al. state that there is a possibility that Axl is involved in vascular structure and function (page 1176, col. 2, second full paragraph). However, O'Donnell et al. also specifically state that "the major role of Axl-Gas6 interaction may therefore be in survival of the vasculature under conditions of cellular stress or injury" and "may also promote survival of activated endothelial cells, and perhaps other Axl-positive cells, within the hostile environment of the inflamed rheumatoid joint" (page 1179, col. 1, emphasis added). Finally, O'Donnell et al. suggest that this "survival mechanism normally involved in tissue homeostasis could also contribute to

maintenance of a pathological vasculature" (page 1179, col. 1, emphasis added). Thus, when read as a whole O'Donnell et al. is clearly directed to the role of Axl and its ligand Gas6 in survival or viability of endothelial cells. While endothelial cells are required for angiogenesis, signals that promote the survival or proliferation of endothelial cells do not equate to angiogenic signals (discussed further in Section B, below).

Appellants argue that the Office states that "O'Donnell et al. teaches that Axl may be involved in tube formation during [] angiogenesis" (Office action of November 5, 2010, page 4, second full paragraph). O'Donnell et al. actually state that "homophilic binding between the extracellular domains of Axl has been demonstrated. This suggests a role in cell adhesion which could be relevant to tube formation in angiogenesis. Vascular smooth muscle cell expression has been previously noted in the rat and may suggest involvement of Axl in some other aspect of vascular function" (p. 1176, last 7 lines; emphasis added). O'Donnell et al. further note that Gas6 is a "promiscuous ligand" for the Axl subfamily (which includes Axl, Sky, and Mer tyrosine kinases) and that "Gas6 has been shown to protect a number of Axl-positive cells from stimuli that induce apoptosis" (page 1178, col. 2, second full paragraph). Other "nonmitogenic" effects of Gas6 (such as chemotaxis) may be due to the "promiscuous" effects of Gas6 and not specific to Axl. Thus the suggestion that Axl is involved in cell adhesion, which could be relevant to tube formation, is highly speculative, given that this effect could be mediate by Gas6 through one of its other receptors (such as Sky or Mer).

Appellants argue that the disclosure of O'Donnell et al. is highly similar to that of Healy et al. (Am. J. Physiol. Lung Cell Metabol. 280: L1273-L 1281, 2001), which was previously cited by the Office in a rejection under 35 U.S.C. § 103(a) in combination with Varner and

Cheresh and Klinghoffer et al. (e.g., Office action dated June 23, 2008). Similar to O'Donnell et al., Healy et al. disclose that Gas6 increased cell number and decreased apoptosis of endothelial cells which express Axl polypeptide (e.g., Healy et al., page L1276, col. 2, last paragraph; page L1277, col. 2; and page 1278, col. 2). Healy et al. also disclose that apoptosis plays a role in vascular remodeling associated with tumor angiogenesis (page 1280, last paragraph). However, in the Decision of the BPAI in the previous appeal in this application, the BPAI found that Healy et al. did not provide sufficient motivation for one of skill in the art to assay an angiogenesis marker such as $\alpha v\beta 3$ expression in endothelial cells (BPAI Decision of Appeal 2009-011194, March 16, 2010, page 17, last paragraph; attached). Similarly, although O'Donnell et al. includes speculative statements to the effect that Axl could perhaps play a role in some cellular events that are associated with a number of processes (including, but not limited to angiogenesis), this does not provide sufficient motivation for one of skill in the art to consider that an Axl inhibitor would be an inhibitor of angiogenesis or to assay angiogenesis phenotypes selected from $\alpha V\beta 3$ expression, tube formation, and haptotaxis in a cell-based assay, as in Applicants' claims.

Appellants argue that based on the focus of Mor on using an assay for inhibitors of Axl to identify compounds for use in treating renal fibrosis and glomerulosclerosis, conditions which are not associated with angiogenesis, and the focus of O'Donnell et al. on the role Gas6-Axl in endothelial proliferation and/or survival, one of skill in the art would not have been motivated at the time of Applicants' filing to combine the disclosures of Mor and O'Donnell et al. to develop an assay for inhibitors of Axl that would identify an inhibitor of angiogenesis. Although O'Donnell et al. speculate as to the possible role of Axl and its ligand Gas6 in cellular functions such as cellular adhesion and chemotaxis (which in some instances are involved in

angiogenesis), one of skill in the art would not read this reference as whole as suggesting that inhibitors of Axl will be inhibitors of angiogenesis. Cell adhesion and chemotaxis are cellular functions that occur during angiogenesis, but they also occur in many other processes, such as inflammation and tumor metastasis. Thus, particularly given the focus of Mor on fibrosis and glomerulosclerosis, one of skill in the art would not expect Axl to be involved in angiogenesis based on the speculative statements regarding cell adhesion and chemotaxis found in O'Donnell et al. Similarly, endothelial cell survival or proliferation are cellular functions that occur during angiogenesis, but also occur during other processes, such as maintenance of vascular structure under conditions of cellular stress or injury (as pointed out in O'Donnell et al. at page 1179, col. 1).

Appellants argue that Varner and Cheresh describe the role of αvβ3 integrin in the process of angiogenesis (page 726, fight column) and disclose that an αvβ3 antagonist inhibits angiogenesis (page 726- 727). However, this reference does not teach or suggest a role for Axl polypeptide in angiogenesis. Without a reasonable expectation that Axl is involved in angiogenesis (which is not provided by Mor or O'Donnell et al., alone or in combination), one of skill in the art would not be motivated to measure αvβ3 expression in the assay of Mor. Therefore, the combination of Varner and Cheresh with Mor and O'Donnell et al. does not provide a motivation for one of skill in the art to measure αVβ3 expression in the assay of Mor.

Appellants argue that finally, Klinghoffer et al. merely disclose siRNAs and their use as therapeutics for a wide range of diseases. Like Varner and Cheresh, Klinghoffer et al. does not teach or suggest a role for Axl polypeptide in angiogenesis. Thus, there is no motivation for one

of skill in the art to utilize siRNAs in the assay of Mor to identify inhibitors of angiogenesis, even in combination with the disclosure of O'Donnell et al. and/or Varner and Cheresh.

Appellants' arguments have been considered, but have not been found persuasive. First Appellants appear to be arguing against the references individually and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Additionally, although Mor examines other aspects of Axl function and expression, the publication is relevant for all it contains. Mor clearly indicates that by screening for inhibitors of Axl kinase activity, which is expressed in endothelial cells, that one can identify inhibitors of angiogenesis. See the claims, abstract, and paragraph 0090. Additionally, the teachings of Mor clearly indicate that at the time of the invention was made that the art recognized that factors that affect the growth and survival of endothelial cells would be factors that affect angiogenesis and Mor teaches that Axl activation is a factor that promotes survival of endothelial cells. See paragraphs 0020-0022, 0090 0255 and 0256. Nothing in the disclosure of Mor teaches away from Axl activation being involved in the promotion of angiogenesis or that cell growth and survival are not involved in the formation of new blood vessels, i.e. angiogenesis. One of skill in the art would have recognized at the time the invention was made that based on the disclosure of Mor and O'Donnell et al. that endothelial cell growth and survival are important for angiogenesis because new blood vessels could not form without the growth and survival of new endothelial cells.

Additionally, the teachings of O'Donnell et al. reinforce those of Mor as to the involvement of Axl in angiogenesis. O'Donnell clearly shows that Axl is expressed in endothelial

cells and is involved in their viability and survival, which O'Donnell et al. teaches is a factor important in angiogenesis. See abstract and introduction on pp. 1171-1172. Although O'Donnell et al. only suggests a role for Axl in cell adhesion and tube formation, one of skill in the art would have recognized based on the disclosure of O'Donnell et al. that tube formation is important for angiogenesis and compounds that inhibit tube formation would inhibit angiogenesis. Thus, combining the Axl activity assay of Mor with a tube formation assay as taught by O'Donnell et al. to identify compounds that inhibit angiogenesis would have been obvious because both activities were taught to be involved in angiogenesis associated with Axl and results in both assays would corroborate the activity of the screened compounds.

In regards to Healy et al., the instant rejection is not based on Healy et al. and the obviousness rejection previously reversed by the BPAI did not include Mor, thus the obviousness of the instantly claimed invention based on the teachings of Healy et al. in combination with any of the cited references is not in question here. Furthermore, Healy et al. does not teach away from Axl's role in angiogenesis as indicated in the Appellants citations of Healy et al. which support Axl's role in angiogenesis.

Additionally, with regard to Varner and Cheresh and Klinghoffer et al., although they do not specifically point to Axl's role in angiogenesis, the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Given that Mor teaches that identification of Axl kinase activity inhibitors will identify angiogenesis inhibitors and is important in endothelial cell survival and Varner and Cheresh teach that expression of integrin $\alpha v\beta 3$ is important in endothelial cell survival, see p.

726-727, it would have been obvious to assay $\alpha v\beta 3$ expression with the Axl activity of Mor to screen for angiogenesis inhibitors as both were known to play a role in angiogenesis and the combined results would more clearly indicate the compounds activity toward angiogenesis. Furthermore, given the advantages of RNAi/siRNA taught by Klinghoffer et al. over other types of polynucleotide inhibitors for specific alteration of gene expression, it would have been obvious to screen an RNAi molecule in the combined assays suggested by the combined art for their ability to inhibit angiogenesis. Thus Appellants' arguments are not found persuasive.

B. No Reasonable Expectation of Success

Appellants argue that an additional element of a prima facie case of obviousness is that the prior art must support a reasonable expectation of success for achieving the invention. "The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." M.P.E.P. § 2143.02 (emphasis added). The references cited in the rejection of claims 1, 14-18, 27, 41-44, 54, and 55 under 35 U.S.C. § 103(a) do not support a reasonable expectation of success for achieving Applicants' claimed invention, in light of the knowledge of one of skill in the art. Therefore, the Office has not met this requirement for establishing prima facie obviousness.

Appellants argue that as discussed above in Section A, both Mor and O'Donnell et al. are strongly focused on cell proliferation and survival with respect to the cellular function of Axl (e.g., Mor, paragraphs [0036], [0059], [0069], [0161-1063], and [0241]; O'Donnell et al., page 1172, col. 1, first paragraph; page 1174, col. 2, last paragraph to page 1176, col. 2, top; page 1179, col. 1). Neither Varner and Cheresh nor Klinghoffer et al. provide any information on the potential cellular function of Axl. Therefore, one of skill in the art would not have had a

reasonable expectation of success for achieving the claimed methods for identifying a compound that inhibits angiogenesis by combining the teachings of these references, particularly when each reference is read as a whole.

Appellants argue that is not predictable that a compound that inhibits cell proliferation, even endothelial cell proliferation, is also a compound that also inhibits angiogenesis. For example, Frater-Schroder et al. (Proc. Natl. Acad. Sci. USA 84:5277-5281, 1987; cited in the Office action of December 12, 2007) discloses that tumor necrosis factor α (TNF-α) inhibits proliferation of endothelial cells in culture, but stimulates neovascularization in an in vivo assay (e.g., page 5277, col. 2, first paragraph; page 5278, col. 1-2; page 5279, col. 1, first full paragraph). This property of inhibition of endothelial cell proliferation in culture, but stimulation of angiogenesis in vivo, is not unique to TNF-α. Frater-Schroder et al. point out that transforming growth factor β (TGF-β) exhibits these same characteristics (e.g., page 5279, col. 2, third full paragraph and page 5280, col. 1-2).

Appellants argue that Mor states that inhibitors of Axl identified in the assays disclosed in that reference could be used for treatment of conditions "where preventing or reducing proliferation of endothelial cells is desired" (Mor, paragraph [0090]) and merely makes the conclusory statement that antagonists of Axl could be anti-angiogenic drugs. There is no disclosure that Axl is involved in any processes related to angiogenesis. Mor only provides data showing that Axl expression is increased in tubular epithelial cells in fibrotic kidney regions and suggests that Axl is involved in cell proliferation in these regions (Mor, paragraphs [0239-0240]). As discussed above, it is not predictable that an inhibitor of cell proliferation is an inhibitor of angiogenesis. Therefore, one of skill in the art would not have had a reasonable

expectation that an inhibitor of Axl would be an inhibitor of angiogenesis at the time of filing of the present application.

Appellants argue that the data presented by O'Donnell et al. is entirely focused on the expression of Axl in synovial tissue and the ability of Axl's ligand Gas6 to protect human umbilical vein endothelial cells from apoptosis (O'Donnell et al., pages 1174-1176). O'Donnell et al. provide two statements regarding the ability of Gas6 to promote cell adhesion between cells expressing Axl and suggest that this could play a role in tube formation or chemotaxis (page 1176, col. 2, second full paragraph). However, these statements are entirely speculative and are not supported by any evidence in O'Donnell et al. (or the other references cited by the Office). O'Donnell et al. also note that Axl was previously found to be expressed in vascular smooth muscle cells in the rat and "may suggest involvement of Axl in some other aspect of vascular function" rather than angiogenesis (O'Donnell et al., page 1176, last 4 lines).

Appellants argue that when read as a whole, both Mor and O'Donnell et al. only disclose that Axl plays a role in cell proliferation and survival. As it is not predictable that a compound that inhibits endothelial cell proliferation also inhibits angiogenesis, one of skill in the art would not have had a reasonable expectation of success that the assays of Mor could be used to identify a compound that inhibits angiogenesis, for example, utilizing tube formation or chemotaxis, which are mentioned only in passing by O'Donnell et al.

Appellants argue that furthermore, Varner and Cheresh disclose the potential role of the integrin $\alpha v\beta 3$ in tumor cell proliferation and survival (e.g., Varner and Cheresh, page 725, col. 2, third full paragraph and page 727, col. 1-2) and tumor angiogenesis (e.g., Varner and Cheresh, page 726, col. 2, second full paragraph to page 727, col. 1, second paragraph). Klinghoffer et al.

discuss use of siRNA for modulating biological signal transduction (Klinghoffer et al., paragraph [0028]). Neither Varner and Cheresh nor Klinghoffer et al. disclose any potential cellular function for Axl, let alone a potential role in angiogenesis. Thus, the combination of these two references with Mor and O'Donnell et al. would not have provided one of skill in the art with a reasonable expectation of success for achieving the claimed methods for identifying a compound that inhibits angiogenesis.

Appellants' arguments have been considered, but have not been found persuasive. Mor clearly indicates that by screening for inhibitors of Axl kinase activity, which is expressed in endothelial cells, that one can identify inhibitors of angiogenesis. See the claims, abstract, and paragraph 0090. One of skill in the art could have readily performed the routine Axl kinase assay taught by Mor as the skill in the art was high at the time of the invention. Furthermore, although one of skill in the art would have recognized the importance of cell survival and proliferation in angiogenesis in view of the cited art, Mor does not teach that a survival or cell proliferation assay must be performed to identify the angiogenesis inhibitors as the invention is directed to identifying Axl activity and kinase inhibitors. See the claims. Additionally, one of skill in the would have been able to perform tube formation assays and determine $\alpha v\beta 3$ expression based on the teachings of O'Donnell et al. and Varner and Cheresh and would have recognized inhibitors of these endothelial cell phenotypes would predictably be inhibitors of angiogenesis based on the disclosures. Furthermore, the assay claimed is a screening assay for angiogenesis inhibitors, thus no foreknowledge of a compound's activity or effect on Axl or angiogenesis, such as the RNAi molecules taught by Klinghoffer et al., is required to perform the claimed screening assay. Similarly, although compounds like TNF-α taught by Frater-Schroder

et al., may have variable in vitro and in vivo effects on endothelial cell growth and survival, no foreknowledge of a compound's activity or effect on Axl or angiogenesis is required in the claimed method. Additionally, it is noted that Frater-Schroder et al. do not teach or suggest that endothelial cell growth and survival are not important for angiogenesis, rather that the differential effects observed in vitro and in vivo with TNF-α were surprising and TNF-α stimulated the ingrowth of blood vessels in vivo and enhanced bFGF induced angiogenesis in vivo, possibly by an inflammatory mechanism. See p. 5280. Thus, given the teachings of the art and the routine nature of the assays one of skill in the art would have had a reasonable expectation of success of making and using the claimed method to identify inhibitors of angiogenesis for the reasons previously set forth and above.

C. Obviousness under the Post-KSR v. Teleflex Guidelines

Appellants argue that Following the Supreme Court decision in KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007), the Office published Examination Guidelines which included exemplary rationales that may support a conclusion of obviousness (72 Fed. Reg. 57526-57535,

Appellants argue that October 10, 2007; "Guidelines"). These rationales have subsequently been incorporated in the M.P.E.P. at § 2143. The rationales provided in the Guidelines and M.P.E.P. § 2143 that may be relevant to the pending appeal include "(A) combining prior art elements according to known methods to yield predictable results'; (B) simple substitution of one known element for another to obtain predictable results'; ... (E) 'obvious to try' - choosing from a finite number of identified predictable solutions, with a reasonable expectation of success; ... (G) some teaching, suggestion, or motivation in the prior

art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention" (M.P.E.P. § 2143, emphasis added). Applicants have based their arguments above on the last rationale (G), as this appears to be the rationale set forth in the Office action of November 5, 2010, and the Advisory Action of January 27, 2011.

Appellants argue that the arguments set forth above demonstrate that the Office has not made a prima facie case of obviousness, even if one of the other rationales set forth in the Guidelines and M.P.E.P. § 2143 were applied. Each of the rationales set forth as (A), (B), and (E) requires that the combination of elements yield **predictable results** or a **reasonable expectation of success**. As discussed in part B above, prior to the filing of this application, one of skill in the art would not have had any reasonable expectation of success in achieving Applicants' claimed methods based on the cited references. Therefore, even if one of the other rationales is applied, the Office has not met its burden to demonstrate a prima facie case of obviousness in rejecting claims 1, 14-18, 27, 41-44, 54, and 55.

D. Conclusion

Appellants argue that they have shown that the Office has not established a prima facie case of obviousness, because one of skill in the art would not have been motivated to combine the cited references nor have a reasonable expectation of success to arrive at Applicants' claims. Therefore, the claims are not obvious in light of the cited references.

Appellants' arguments have been considered, but have not been found persuasive. In sections C and D Appellants are summarizing their previous arguments. Thus, for the reasons set forth above the arguments are not found persuasive and the claimed invention is obvious in view

of the cited art for the reasons previously set forth. Furthermore, the combination of elements would yield predictable results and would have a reasonable expectation of success for the reasons previously set forth and above.

(11) Related Proceeding(s) Appendix

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/PETER J REDDIG/

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